REMARKS

Applicants have canceled pharmaceutical composition claims 7 and 8 and added new claim 11 directed to a pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable salt thereof. Applicants have amended claims 9 and 10 to delete the term "including".

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 7-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has stated that it is "not known which disorder or condition is mediated by ORL1-receptor and it endogenous ligands and which ones are not." Further, the Examiner states that the term "including" renders the claims indefinite "because it is unclear whether the limitations . . . are part of the claimed invention." Further, the Examiner states that the phrases "useful as" and "useful for" are improper.

Applicants traverse in part and have amended the claims to overcome this rejection. As claims 7 and 8 have been canceled, this rejection remains only with respect to claims 9 and 10.

One of skill in the art in the pharmaceutical arts, particularly one well versed in the opioid therapeutic field, would understand quite well the diseases, disorders or conditions "which can be effected or facilitated by activating ORL1-receptor". There are a number of disorders and conditions that are set forth quite adequately to support this language at pages 4 to 6 of the specification. In addition, Applicants have amended claims 9 and 10 to delete the term "including" and have canceled claim 8 which contained the terms "useful as" and "useful for".

Accordingly, in view of the amendments to the pending claims 9 and 10, Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 7-10 under 35 U.S.C. § 112, first paragraph, because the specification while being enabling as a method of treating pain, does not reasonably provide enablement for the treatment of all other indications recited in the claims. The Examiner cites to the examples of "Alzheimer's disease, tolerance to narcotic analgesics, dependence on narcotic analgesics, Parkinson's disease, etc." Further, the Examiner urges that there are no known compounds of similar structure to those of the present invention "which have been demonstrated to treat" these diseases.

Applicant traverses. The Examiner has presented no sufficient reason to doubt the objective truth of the statements that compounds which modulate ORL1-receptors are useful in the treatment of diseases, disorders or conditions referred to in the claims.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. U.S. v. Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); MPEP § 2164.01. The factors regarding undue experimentation may include: (a) the breadth of the claims, (b) the nature of the invention, (c) the state of the prior art, (d) the level of one of ordinary skill, (e) the level of predictability in the art, (f) the amount of direction provided by the inventor, (g) the existence of working examples and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

MPEP § 2164.04 states that "In order to make a rejection [under § 112, first paragraph], the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510,1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)." (emphasis added) Further, the burden is on the Examiner to come forth with evidence to establish a *prima facie* case of nonenablement. Ex parte Hitzeman, 9 U.S.P.Q. 2d 1801, 1822 (Pat. Off. Bd. App. 1988); In re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); In re Marzocchi, 169 U.S.P.Q. at 270. Without establishing a *prima facie* case of nonenablement the statement contained an Applicant's specification must be taken to be true. In re Marzocchi, 169 U.S.P.Q. at 269-270.

Applicant urges that the Examiner has not properly set forth a case indicating a lack of enablement under Section 112. Applicant has provided generic and specific disclosure of

compounds which are asserted to have certain therapeutic activity useful in the treatment of a number of conditions. The Examiner has not questioned at all the ability of one of skill in the medicinal chemistry arts to prepare and use these compounds in view of that part of the disclosure drawn to chemical synthetic procedures.

Rather, the basis for the Examiner's Section 112 rejection is simply a blanket statement that the claimed methods are not enabled the utility has not previously been "demonstrated" to treat these diseases.

The Examiner imposes a mighty burden indeed on Applicant and one that is not required by the Patent Law. Such a burden would prevent almost any entity from applying for a patent application without exhaustive investigation of mechanism and therapeutic efficacy. Definitive proof of mode and efficacy is not required by the Patent Law to satisfy the enablement requirement of Section 112. The Examiner is referred to the controlling Federal Circuit case of In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) regarding a similar Section 112 rejection by the examiner in that case who had stated that "even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful."

The Court in In re Brana strongly objected to such a rejection, reiterated the holding of In re Marzocchi (cite directly above), and continued stating that:

> "From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 USPQ at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See* In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)." 34 USPQ2d at 1441.

However, the Examiner in this case, just as the examiner in Brana not met this initial burden. The Examiner in this case has cited no references that would question the usefulness of any of the ORL1-receptor agonist compounds as a therapeutic agent nor has provided any other evidence to cause one of skill in the art to question the asserted utility of Applicant's compounds. Rather, there is nothing in the nature of Applicant's invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. Analogous to the Brana Court's reasoning, the treatment of a set of central nervous system diseases, disorders or conditions, do "not suggest an inherently unbelievable undertaking or involve implausible scientific principles." *See*, In re Jolles, 628 F.2d at 1327, 206 USPQ at 890. As the Court reasoned in Brana:

> "Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The

> PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. See In re Marzocchi, 439 F.2d at 224, 169 USPQ at 370." 34 USPQ2d at 1441.

Likewise, Applicant's disclosure should be considered presumptively correct with respect to the diseases, disorders and conditions iterated in the specification and claims as treatable by use of ORL1-receptors agonist compounds of the invention. Like the court in Brana, evidence of "test results showing that several compounds within the scope of the claims exhibited significant . . . activity . . . Such evidence alone should have been sufficient to satisfy applicants' burden." *See*, 34 USPQ2d at 1441.

The Examiner, like the Board in Brana here has confused:

> "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See* Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings."). 34 USPQ2d at 1442.

Further, the Examiner should acknowledge, as did the Brana Court, that "one who has taught the public that a compound exhibits some desirable pharmaceutical property . . . has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *See*, In re Krimmel, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961).

The Examiner simply cannot maintain the enablement objections under the pretext that the asserted utility of the claimed compounds lacks credibility. As noted above, the Marzocchi court, and reiterated by the Federal Circuit in Brana, stated that, "the only relevant concern of the Patent Office should be over the *truth* of any such assertion. The first paragraph of § 112 requires nothing more than objective enablement." 169 USPQ at 369. Consequently, Applicant's asserted utilities should be respected in the absence of anything more than Examiner speculation to refute it.

Applicant should be able to rely on its asserted presumptively correct utility (in the words of the Brana court) in the absence of any substantial and convincing showing by the Examiner that would place that utility in doubt. The patent literature cited above clearly provides support for a reasonable nexus between the ORL1-receptors modulating activity of the compounds of the invention and the diseases, disorders and conditions set forth in the claims.

Further, the criteria under 35 U.S.C. § 112, first paragraph, relating to enablement and "undue experimentation" from the Wands case weigh heavily in favor of a finding that the present claims are fully enabled by the instant specification. Applicant has provided literature references to known assays for the *in vitro* and *in vivo* testing of the ORL1-receptors modulating activity of compounds of the invention at pages 35-39 of the specification. These assays, which provide means to detect the ability of a compound to bind ORL1-receptors (as well as determining the selectivity of the compouds amongst various other opioid receptors), as well as function and analgesic tests, would be considered routine by one of ordinary skill the pharmaceutical art. The Examiner has not shown that these assays are anything other than routine.

As the patent law acknowledges, testing such as has been referenced is sufficient to enable the compounds of the pending claims, if it is merely routine. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 190 USPQ 214, 217-19 (CCPA 1976)). Furthermore, Applicant has provided in the specification the results of some of these assays on the compounds of the invention at pages 36-37:

> "In this testing, all the compounds prepared in the working examples appearing hereafter demonstrated higher affinity on ORL1-receptors than on mu-receptors as defined by the following equation. IC_{50} (ORL1-receptors) nM/IC_{50} (mu-receptors) nM <1.0"

In summary, an examination of the criteria relating to "undue experimentation" from Wands weighs in favor of a finding that the present claims are fully enabled by the instant specification. The claims are not so broad as to include subject matter which would confuse one of ordinary skill in the art of chemical synthesis or pharmaceutical art. (critera (a)) The relatively straightforward nature of the structure of the compounds in view of the state of the synthetic chemical arts weighs in favor of the ready preparation of compounds within the scope of the genus of claim 1. (criteria (b)-(f)) There are a number of working examples (21 Examples) providing ample exemplification of the scope of the compounds. (criteria (g)) Finally, there are a number efficiently performed assays provided in the specification (pages 35-39) to demonstrate for the compounds of the invention the desired ORL1-receptor modulating activity that is art-recognized to have a nexus with the treatment of certain CNS disease, disorders and conditions. (criteria (h)).

As all of the Wands criteria weigh in favor of a finding of no undue experimentation and the Examiner has not advanced any other adequate reasons to establish that a person skilled in the art could not use the genus of claim 1 as a whole without undue experimentation, Applicant requests that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Objection under 37 C.F.R. § 1.75

The Examiner has objected to claims 7 and 8 under 37 C.F.R. § 1.75 as being substantial duplicates.

Applicants have canceled claims 7 and 8, replacing the subject matter with new claim 11. Accordingly, the Examiner's objection is rendered moot.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-10 as being unpatentable over U.S. Patent No. 6,172,067 ("Ito et al."). The Examiner urges that Ito et al. "teaches a generic group of benzimidazole derivatives which embraces applicants' claimed compounds" and that the present claims "differ from the reference by reciting specific species and a more limited genus than the the reference." The Examiner asserts that it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties"

Applicants traverse. The present invention is not obvious in view of the Ito et al. reference. There must be some motivation or suggestion to make the claimed invention in light of the prior art teachings. *In re Brouwer*, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

There is no recitation of the presently claimed compounds in that reference, nor is there any suggestion or motivation within that reference to motivate one of ordinary skill to make the particular compounds of the present invention. The Examiner has not pointed to a single passage with Ito et al. that would provide the necessary suggestion to the skilled artisan.

There is no specific part of the cited references that would lead one of ordinary skill in the art to choose the specific invention claimed here. In the absence of a specific motivation in the art itself to give one of ordinary skill a reasonable expectation of success, there can be no assertion of obviousness.

Accordingly, Applicants request withdrawal of the Examiner's rejection under 35 U.S.C. § 103(a).

Double Patenting Rejection

The Examiner has rejected claims 1-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,172,067. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the two sets of claims overlap substantially."

Applicants traverse. For reasons stated above in response to the Examiner's rejection under 35 U.S.C. § 103(a), Applicants maintain that the present invention is not obvious in view of the Ito et al. reference and hence cannot be the basis of the present double-patenting rejection. As there is no basis for asserting the obviousness of the particular compounds of the present invention, Applicants request withdrawal of this rejection.

In view of the amendments to the text and the claims, Applicant believes that he has placed the application in condition for allowance respectfully requests issuance of a notice of allowance for the application.

Respectfully submitted,

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APPENDIX TO RESPONSE AND AMENDMENT

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IN THE CLAIMS

Cancel claims 7-8. Add new claim 11.

9. (Amended) A method of treating a disorder or condition, or anesthetizing a mammal [~~including a human~~], the treatment and anesthetization of which can be effected or facilitated by activating ORL1-receptor in a mammal [~~including a human~~], comprising administering to a mammal in need of such treatment an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

10. (Amended) A method for treating a disorder or condition in a mammal [~~including a human~~], where the disorder or condition is selected from the group consisting of neuropathic pain, inflammatory diseases, inflammation-related hyperalgesia, eating disorder, arterial blood pressure disorders, tolerance to narcotic analgesics, dependence on narcotic analgesics, anxiety, stress disorders, psychic trauma, schizophrenia, Parkinson's disease, chorea, depressant, Alzheimer's disease, dementias, epilepsy and convulsions, or for anesthetizing a mammal including a human, or for alleviating pain, producing a neuroprotective effect, enhancing analgesic, controlling water balance, hearing regulation, controlling sodium ion excretion or ameliorating brain function in a mammal [~~including a human~~], comprising administering to said mammal an effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Add new claim 11.

11. (New) A pharmaceutical composition comprising an amount of a compound according to claim 1, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.